Kantoff, P.W., et al. article in the *Journal of Clinical Oncology*, Vol. 17, No. 8 (August), 1999:pp 2506-2513, at page 2509.

As set forth in the attached Declaration by Dr. Jones, the significant drops in PSA for the treated patients is surprising because they were each given only one dose of the Rhodamine-123 in the course of clinical trials to establish toxicity limits. Even so, there is evidence that at least two of the 12 patients will have their lives significantly extended beyond the normally expected limits because PSA levels dropped more than 50% for those two patients.

In view of the evidence set forth in the Declaration, the rejection of claims 1-27 should be withdrawn.

As is well known, prostate cancer kills thousands of men each year. If the cited Arcadi references of 1986 and 1990 made it obvious that prostate cancer can be successfully treated with Rhodamine-123, that treatment would have been widely used long ago.

Unfortunately, even through *in vitro* and animal laboratory tests of a drug may produce encouraging preliminary results, many such drugs prove to be ineffective for human treatment for various reasons, such as unexpected toxicity, or other unanticipated reaction. For example, see the enclosed copy of *The Economist*, September 20, 1997, page 91, which reports:

> "At the start of chemotherapy, tumor cells are sensitive to the various chemicals designed to reign them in and kill them off. During the course of treatment, however, they often develop resistant to a whole class of drugs at once -- a phenomenon known as multidrug resistance, which makes the cancer hard to treat. One reason for this is that the tumor cells have more ways of getting rid of foreign molecules than healthy cells do."

Although prior art might make it obvious to try drugs such as Rhodamine-123 in treating prostate cancer, that does not make applicant's claimed invention obvious under 35 USC

Section 103. That has long been the law. *See, Uniroyal v. Redkin-Wiley* 5 USPQ 2d 145 (Fed. Cir., 1988) where the U.S. Court of Appeals stated at page 1440:

> "Finally, the District Court in its validity discussion has erred in other respects. It appears to have applied the often rejected obvious to try standard when it says that after combining Constantin, the Marilyn Study and Stan, it would be a matter of experimentation in order to extract the exact perimeters . . . that would make the device work."

Even though one of ordinary skill might have been inspired by Dr. Arcadi's 1986 and 1990 publications to try Rhodamine-123 in treating human prostate cancer, there is no assurance the drug would work, absent the detailed teachings claimed in the present application.

In view of the early success indicated by the limited clinical trials to date, the claims in this application should be allowed.

Alternatively, applicant submits herewith a Petition for Suspension of Prosecution under 37 CFR 1.103. The Petition for Suspension of Action is presented as a separate paper, accompanied by the petition fee, as required by U.S. P.T.O. notice of July 6, 1992 (1141 O.G. 63).

Respectfully submitted,

CHRISTIE, PARKER & HALE, LLP

By _____

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RWJ/cls
Enclosure: Declaration
copy of *The Economist*

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Cell biology

The secret of the vaults

Inside the cell is a mysterious structure known as a vault. Only now are biologists beginning to understand the things it does, and one of them seems to be to make cancer cells resistant to drugs

SHRUNK to one ten-millionth of your size, you could do what cell biologists can only dream of. You would be small enough to fit inside a cell, able to wander about and observe the bustling, complex and often beautiful machinery that is the basis of life. Better still, you would be able to see what all the different machinery does. For one of the frustrations of cell biology is that, all too often, a cell's components are hard to observe in action. As a result, detecting what a new structure does relies heavily on circumstantial evidence.

The bulk of such detective work was done in the 1940s and 1950s, when most of the large components of cells were discovered. But only within the past decade has an intriguing new entity known as the vault appeared under the electron microscope. Researchers have worked out the structure of vaults, but are only just beginning to understand what they do. Three independent lines of evidence suggest that they are involved in shuttling molecules—including the drugs used in chemotherapy—around the interiors of cells.

Barrels of mystery

Vaults have been found in every living thing scientists have looked at that is larger than a yeast—from slime moulds and electric eels to rats and humans. The genes for vaults are almost the same among all these different organisms—a good indication to evolutionary biologists that whatever vaults do, it is crucial for the cell.

When they are whole, vaults look like barrels—though they are only 35 by 65 millionths of a millimetre across. They are, nevertheless, relatively large by cellular standards—three times the size of ribosomes (the factories that produce proteins). And individual cells often have several hundred of them—so they are not only large, but abundant. That they went unnoticed for so long testifies to the difficulties of finding something in a cell unless you already know what to look for.

Each of the caps of a vault's barrel is made from a ring of proteins. Hooked on to these rings are the eight staves of the barrel. A single stave is composed of six much larger proteins, known as the major vault proteins. Split the barrel through its equator, and each of the halves falls open into a symmetrical flower-like structure, with the major vault proteins now making up eight "petals". Some researchers, including Nancy Kedersha, a biologist at ImmunoGen (a biotechnology company in Cambridge, Massachusetts) who was one of the discoverers of vaults, think they regularly switch from open (ie, flowers) to closed (ie, barrels).

From their barrel-like structure, it is tempting to think that vaults could serve as containers for other molecules—opening up into flowers when their cargoes need to be released. Although they occur in most cells, they crop up in particularly large numbers in cells of three kinds: those that move a lot, those that transport molecules in and out a lot, and tumour cells that are resistant to many different drugs (which are usually cells that are able to get rid of lots of foreign toxins). This is the first line of evidence that they may be involved in the transport of molecules.

The second is that they are strong candidates to form things known as nuclear-pore-complex plugs. Nuclear-pore complexes are elaborate protein scaffolds that sit in the membrane around a cell's nucleus. They help molecules to cross this membrane and enter the nucleus. Leonard Rome and Valerie Kickhoefer, biochemists at the University of California, Los Angeles, and their colleagues reckon that vaults are exactly the right size and shape (they have the correct eightfold symmetry) to form the central plugs of these complexes. They would act, the researchers believe, by opening and closing like a sort of airlock.

Moreover, when stained and observed through a microscope, vaults cluster around, and sometimes on, the nuclear-pore complex. These observations are not, however, enough to convince the sceptics. At the moment, the notion that vaults are the unidentified plugs of the complex is still controversial.

But perhaps the most compelling evidence that vaults are involved in shuttling molecules comes from a different line of reasoning altogether. Rik Scheper and his colleagues at the Free University of Amsterdam inadvertently stumbled across the major vault protein when they were looking for proteins important in drug resistance in tumour cells.

At the start of chemotherapy, tumour cells are sensitive to the various chemicals designed to rein them in and kill them off. During the course of treatment, however, they often develop resistance to a whole class of drugs at once—a phenomenon known as multidrug resistance, which makes the cancer hard to treat. One reason for this is that tumour cells have more ways of getting rid of foreign molecules than healthy cells do.

The best-studied method is for a cell to increase the number of molecular pumps in its outer membrane. These pumps are able to expel toxins from the cell. But Dr Scheper and his colleagues found a new protein that becomes much more common in tumour cells when multidrug resistance appears. To the researchers' surprise, when they compared the sequence for their new protein with those already in the public databases, they discovered that it was actually the major vault protein.

To both Dr Scheper and Dr Rome, this provides further proof that vaults are shuttles—in this case carrying poisons from the nucleus to the vesicles that act as a cell's waste-disposal units. The circumstantial evidence is intriguing: as well as being more abundant in tumours than in ordinary cells, vaults, to Dr Scheper's eye, seem to congregate around the vesicles. Thus, the researchers reckon that when a tumour cell is under pressure from foreign toxins it starts to make more vaults to help get rid of the unwelcome molecules.

Biologists are certain that this trail of clues will eventually lead to a far better understanding of what happens inside cells. They are now trying to make a film of vaults in action. Until then, though, they must long for a potion labelled "drink me", to shrink themselves to a size that would let them take a ride inside a shuttling vault.